REMARKS

A. BACKGROUND

Applicants wish to express appreciation to the Examiner and his supervisor for taking the time to discuss issues raised in the Office Action during the Examiner Interview held April 27, 2011. By this paper, claim 1 was amended and no claims were added or cancelled. Accordingly, claims 1, 2, 7, and 14 are currently pending.

Applicants submit that this amendment is suitable for entry after final rejection under 37 C.F.R. § 1.116 because it does not raise new issues relating to patentability and because it either places the application in condition for allowance or in better condition for appeal.

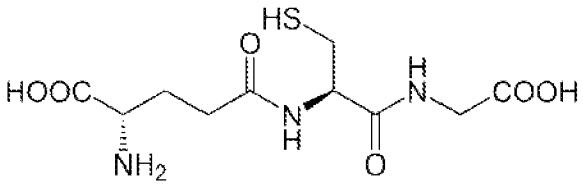
B. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 2, 7, and 14 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite because the previous amendment removed the phrase "to a subject". During the Examiner Interview, the Examiner recommended amending claim 1 to recite the phrase "to a subject in need thereof". Because the amendment to claim 1 was made solely to address the rejection under 35 U.S.C. § 112, second paragraph, and not to distinguish over the cited art, the amendment to claim 1 does not raise any new issues relating to patentability and is therefore suitable for entry after final rejection under 37 C.F.R. § 1.116.

C. CLAIM REJECTION UNDER 35 U.S.C. § 103

The Office Action rejects claims 1, 2, 7 and 14 under 35 U.S.C. § 103(a) as being unpatentable over *Schlag* et al. (US 6,358,918) ("*Schlag*") in view of *Hallström* et al (*Hallström* et al. (2002) *Circulation*, 105, 3032-3038) ("*Hallström*"). Applicants respectfully traverse this rejection because, as will be shown below, the combination of *Schlag* and *Hallström* fails to teach or suggest the combination of elements recited in claims 1, 2, 7 and 14. The Office Action therefore fails to state a *prima facie* case of obviousness relative to the pending claims. In addition, or in the alternative, claims 1, 2, 7 and 14 are unobvious over the combination of *Schlag* and *Hallström* because they define an invention that provides surprising and unexpected results relative to the teachings of *Schlag* and *Hallström*, which objectively rebuts *prima facie* obviousness to the extent a case has been made, a point which Applicants do not concede. Reconsideration and allowance of the presently pending claims is respectfully requested.

Claim 1 is directed to a method for the treatment of ischemia. The method of claim 1 as amended comprises administering a pharmaceutical preparation to a subject in need thereof comprising a therapeutic protein having nitrosated SH-groups, wherein the therapeutic protein is S-nitroso albumin and "reduced glutathione". Thus, claim 1 requires administering both S-nitroso albumin and reduced glutathione to a subject to treat ischemia. Applicants also note that the term "reduced glutathione" is understood to mean GSH, as opposed to S-S linked, or oxidized, glutathione (*i.e.*, GSSH). According to Wikipedia, glutathione in its reduced state has the following molecular structure:



http://en.wikipedia.org/wiki/Glutathione.

Reduced glutathione is characterized as having a single thiol group (-SH) bonded to a carbon atom, as shown in the molecular structure. Reduced glutathione does not have an S-nitroso group in place of the thiol group, as would be present if it were nitrosated. Indeed, reduced glutathione is the preferred example of "compounds containing thiol groups" (Application, p. 3, ln. 22-30) and is not described as having been nitrosated so as to replace the single thiol group with an S-nitroso group. Only albumin contains S-nitroso groups according to claim 1.

In rejecting the claims over *Schlag* and *Hallström*, the Office Action initially interprets the relevant teachings of *Schlag* as follows:

> Schlag et al. teach a method of treating an ischemia (cerebral ischemia) comprising administering to a patient in need thereof a pharmaceutical composition comprising at least one (plurality) [see patent claim 16, line 4] thiol nitrosated (i.e., S-nitroso) thiol-goup-containing proteins, wherein 'at least one' encompasses more than one S-nitroso-proteins that include S-nitroso-albumin (patent claims 21). This is applied to instant claim 1….
>
> Schlag et al. do not expressly disclose or provide working example for combined use of S-nitroso-albumin (S-NO-HAS) and S-nitroso-glutathione (GSH) for treating ischemia.

Office Action, pp. 3-4 (emphasis in original).

In response, Applicants agree with part of the Examiner's characterization of *Schlag* but disagree with other parts as being technically incorrect. First, Applicants agree with the Examiner that *Schlag* discloses the use of a "plurality [of] thiol nitrosated (i.e., S-nitroso) thiol-goup-containing proteins, wherein 'at least one' encompasses more than one S-nitroso-proteins". However, Applicant does not agree with the Examiner's assertion that *Schlag* suggests the specific combination of "S-nitroso albumin" and "S-nitroso-glutathione". As pointed out in the previously filed amendment, *Schlag* teaches that "[a]ccording to the present invention, high-molecular proteins are preferred over low-molecular proteins, such as, e.g., glutathione." Col. 2, ln. 60-62. While this teaching does not entirely foreclose the use of glutathione, it certainly does not suggest the specific *combination* of S-nitroso albumin and S-nitroso glutathione. *Schlag* discloses dozens of different proteins that can be used which, if combined together in all possible combinations, would yield hundreds, if not thousands, of possible combinations. At best *Schlag* discloses a very broad genus of different combinations of S-nitroso proteins but fails to disclose a narrow species that includes the specific combination of S-nitroso albumin and S-nitroso glutathione.

According to well-established case law, disclosure of a broad genus of possible combinations does not necessarily disclose any particular species of combinations unless the genus is relatively small (*e.g.*, 20 or less). *See In re Petering,* 49 C.C.P.A. 993, 301 F.2d 676, 681, 133 USPQ 275, 280 (1962). If there is a vast number of possible combinations, the genus in a prior art patent does not disclose a particular species in a later-filed patent application unless the patent describes "specific preference" that reduce the number of possible combinations and directly lead to the later claimed species. *See id.*

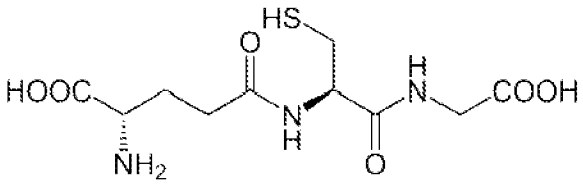
Applying the rule articulated in *In re Petering* to the present case, it is clear that the "specific preference" in *Schlag* teaches away from rather than directly leads to the specific combination of S-nitroso albumin and S-nitroso glutathione. As taught in *Schlag*, "high-molecular proteins are preferred over low-molecular proteins, such as, e.g., glutathione." Col. 2, ln. 60-62. Therefore, among the hundreds or thousands of possible protein combinations in *Schlag*, the stated "preference" of *Schlag* would not lead to the selection of S-nitroso albumin and S-nitroso glutathione to treat ischemia as alleged in the Office Action.

Hallström ("S-Nitroso Human Serum Albumin Treatment Reduces Ischemia/Reperfusion Injury in Skeletal Muscle via Nitric Oxide Release") likewise fails to teach or suggest the

specific selection of S-nitroso albumin and S-nitroso glutathione to treat ischemia and, in fact, only discloses the use of "S-nitroso human serum albumin". *Hallström* merely identifies the fact that both reduced and oxidized glutathione exist naturally in the body in specific ratios and that such ratios are altered when a person is given S-nitroso human serum albumin. *Hallström*, Abstract; p. 3036, right column, first paragraph.

In view of the foregoing, because *Schlag* neither teaches nor suggests the specific selection of S-nitroso albumin and S-nitroso glutathione from among the hundreds or thousands of possible combinations of S-nitroso proteins when treating ischemia, and because *Hallström* does not teach or suggest the use of *any* combinations of S-nitroso proteins but only "S-nitroso human serum albumin" by itself, the combination of *Schlag* and *Hallström* does not teach or suggest the specific combination of S-nitroso albumin and S-nitroso glutathione as asserted in the Office Action. For this reason alone, Applicants submit that the Office Action fails to state a *prima facie* case of obviousness relative to the claims as amended and previously presented.

Even assuming for the sake of argument that *Schlag*, as asserted in the Office Action, suggests treating ischemia using a combination of N-nitroso proteins, and that one such combination is "S-nitroso albumin" and "S-nitroso glutathione", the Office Action still fails to state a *prima facie* case of obviousness relative to the claims as previously presented. As discussed above, claim 1 requires administering a pharmaceutical preparation to a subject in need thereof comprising "S-nitroso albumin" and "reduced glutathione". As discussed above, the term "reduced glutathione" is understood to mean the compound have the following molecular structure:



http://en.wikipedia.org/wiki/Glutathione.

Reduced glutathione is characterized as having a single thiol group (-SH) bonded to a carbon atom, as shown in the molecular structure. "Reduced glutathione" does not have an S-nitroso group in place of the thiol group, as would be present if it were nitrosated. Indeed, "reduced glutathione" is described in the Application as the preferred example of "compounds containing thiol groups" (Application, p. 3, ln. 22-30) and is not described as having been

nitrosated so as to replace the single thiol group with an S-nitroso group. Only albumin contains S-nitroso groups according to claim 1. The term "reduced glutathione" does not encompass "S-nitroso glutathione". Accordingly, even if the assertion in the Office Action that *Schlag* suggests treating ischemia with the combination of "S-nitroso albumin" and "S-nitroso glutathione" were correct, such a suggestion would *not* render obvious the combination of S-nitroso albumin" and "reduced glutathione" as recited in claim 1 as previously presented. And to the extent that *Hallström* can be interpreted as somehow suggesting the selection of albumin and glutathione for use in the disclosed S-nitrosation process of *Schlag*, that does not alter the fact that the combination of "S-nitroso albumin" and "S-nitroso glutathione" does not suggest instead using the combination of "S-nitroso albumin" and "reduced glutathione". Accordingly, for this additional reason, the combination of *Schlag* and *Hallström*, based on the interpretation of *Schlag* at page 3-4 of the Office Action, does not render the claims *prima facie* obvious.

Moreover, evidence in the record supports the conclusion that *Schlag* actually teaches away from the combination of "S-nitroso albumin" and "reduced glutathione" when treating a human. According to *Schlag*,

> An advantage of the nitrosated preparation according to the invention also consists in that on account of its high S-nitroso content it can be administered in smaller amounts than preparations having a substantially lower S-nitroso content. *What is also important is that the* ***release of the active NO groups*** *of the proteins used according to the invention takes place over a* ***longer period of time***, and, on the whole, the kinetics of this reaction is advantageous under physiological conditions.

Col. 7, ln. 25-33 (emphasis added). According to *Schlag*, an "advantage" and "important" feature of the "nitrosated preparation according to the invention" is the "release of the active NO groups" is better than in other preparations because it "takes place over a longer period of time". Thus, *Schlag* teaches away from preparations in which "release of the active NO groups … takes place over a [shorter] period of time" (*i.e.*, is accelerated as compared to the "nitrosated preparation according to the invention" of *Schlag*).

According to *Schlag*, the preferred "nitrosated preparation according to the invention" is "N-nitroso human serum albumin", as evidenced by the Examples and other teachings disclosed throughout *Schlag*. Col. 7, ln. 58 – col. 10, ln. 23. As a baseline comparison, *Schlag* therefore teaches away from "nitrosated preparations" in which "release of the active NO groups" is

accelerated compared to "N-nitroso human serum albumin". Because the claimed invention includes a combination that has been shown to accelerate the release of NO compared to N-nitroso human serum albumin by itself, *Schlag* teaches away from the claimed invention.

According to the Application, Example 2 demonstrates an increase in NO release when S-nitroso albumin was administered in combination with reduced glutathione as compared to administering S-nitroso albumin alone. Application, p. 13, ln. 9-18; Figure 2b. Because *Schlag* explicitly teaches that "[w]hat is also ***important*** is that the ***release of the active NO groups*** *of the proteins used* ***according to the invention*** *takes place over a* ***longer period of time***, but because the combination of S-nitroso albumin and reduced glutathione accelerates the release of NO as a function of time (*see* Figure 2b), *Schlag* essentially teaches away from the use of the combination of S-nitroso albumin and reduced glutathione. Because the rejection of the claims relies on *Schlag* as the sole primary reference, and because *Hallström* does not in fact teach or suggest administering the combination of S-nitroso human serum albumin and reduced glutathione, *Hallström* cannot rebut the express teaching away from the claimed combination contained in *Schlag*. For this additional reason, Applicants submit that the claims as previously presented are not prima facie obvious over the combination of *Schlag* and *Hallström*.

Finally, Examples 1-3 of the Application (See Application ¶¶ [0062]-[0076]) describe several different types of synergistic effects that were observed when S-nitroso albumin was administered in combination with reduced glutathione as compared to the administration of S-nitroso albumin alone. As discussed and agreed to during the Examiner Interview, the showing of unexpected (*i.e.*, unpredictable) results could rebut *prima facie* obviousness. In particular, the Examiner's supervisor acknowledged that a showing of unexpected and unpredictable results of using the claimed combination compared to using S-nitroso human serum albumin by itself would be sufficient to overcome *prima facie* obviousness to the extent it exists.

Example 1 demonstrates a drop in blood pressure when S-nitroso albumin was administered in combination with reduced glutathione as compared to administering S-nitroso albumin alone. Example 2 demonstrates an increase in NO release when S-nitroso albumin was administered in combination with reduced glutathione as compared to administering S-nitroso albumin alone. Example 3 demonstrates a drop in platelet aggregation when S-nitroso albumin was administered in combination with reduced glutathione as compared to administering S-nitroso albumin alone. Examples 1-3 of the Application demonstrate the significant benefit of

administering reduced glutathione (*i.e.*, apart from the glutathione that naturally exists in the subject) in combination with nitrosated albumin. Examples 1-3 are a direct comparison between the claimed invention and a technique similar to the one described in *Schlag* and *Hallström* (*i.e.*, administration of S-nitroso human serum albumin by itself). There is no teaching or suggestion in *Schlag*, *Hallström* or any other art of record from which the specific unexpected results shown in Examples 1-3 could be predicted.

Nor does the Office Action cite to any teaching or suggestion in the prior art that administering the combination of S-nitroso albumin and reduced glutathione would result in *any* of a drop in blood pressure (Example 1), an increase in NO release (Example 2), and a drop in platelet aggregation (Example 3), much less all three. Hence, even if it could be shown that the combination of *Schlag* and *Hallström* suggests the use of S-nitroso human serum albumin and reduced glutathione to treat ischemia for the reasons set forth in the Office Action such that the claims are *prima facie* obvious, the showing of not one but three unexpected and unpredictable results is effective to rebut *prima facie* obviousness.

In short, the fact that administering reduced glutathione in combination with S-nitroso albumin provides surprising, unexpected and unpredictable results (*i.e.*, blood pressure drop, increase in NO release, and drop in platelet aggregation) compared to administering S-nitroso human serum albumin by itself as taught in *Schlag* and *Hallström* is objective evidence that the claimed invention is unobvious over the combination of *Schlag* and *Hallström*.

D. CONCLUSION

For at least the foregoing reasons, Applicant respectfully submits that the pending claims are unobvious by the art of record.

In the event the Examiner finds any remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview or which may be overcome by Examiner amendment, the Examiner is requested to contact the undersigned attorney.

The Commissioner is hereby authorized to charge payment of any of the following fees that may be applicable to this communication, or credit any overpayment, to **Deposit Account No. 23-3178**: (1) any filing fees required under 37 CFR § 1.16; (2) any patent application and reexamination processing fees under 37 CFR § 1.17; and/or (3) any post issuance fees under 37 CFR § 1.20. In addition, if any additional extension of time is required, which has not otherwise

been requested, please consider this a petition therefore and charge any additional fees that may be required to **Deposit Account No. 23-3178**.

Dated this 12th day of May 2011.

Respectfully submitted,

/John M. Guynn 36,153/

JOHN M. GUYNN
Registration No. 36,153
WORKMAN NYDEGGER
Attorneys for Applicant
Customer No. 022913
Telephone: (801) 533-9800

3192837_1.DOC